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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/967,263	Applicant(s) O'Brien et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 15, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above, claim(s) *6-18* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed September 15, 2003 (Paper No. 7) in response to the Office Action of August 22, 2003 (Paper No. 6) is acknowledged and has been entered. Claims 1-18 are pending in the application and Claims 6-18 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-5 are currently under prosecution.

2. Applicant's election with traverse of Group 1, claims 1-5 in Paper No 7 is acknowledged. The traversal is on the ground(s) that the invention of Group 2 is very similar to that of Group 1 and the examination of both groups would not impose a serious burden on the examiner. This is not found persuasive because different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

4. The use of trademarks such as Herceptin disclosed on page 4, line 12, of the specification has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Each letter of the trademarks must be capitalized. See MPEP 608.01(V) and 5.

The disclosure is objected to because of the following informalities:

In particular, on page 29, line 20 the specification recites "on1". Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where such informalities may be found.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

7. Claims 1-3 are rejected under 35 USC 112, first paragraph because while being enabling for a method of treating uterine serous papillary carcinoma in an individual in need of such treatment comprising the step of administering HERCEPTIN, does not reasonably provide enablement for a method of treating uterine serous papillary carcinoma in an individual in need of such treatment comprising the step of administering an antibody to HER-2/neu. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating uterine serous papillary carcinoma in an individual in need of such treatment comprising the step of administering an antibody to HER-2/neu. This includes treating with (1) any antibody to HER-2/neu regardless of where it binds on HER-2/neu, (2) regardless of whether it cross reacts with other antigens including EDGF receptor, (3) as drawn in particular to claim 1, regardless of whether the antibody is monoclonal or polyclonal, (4) as drawn to claims

1 and 2, regardless of whether the antibody is humanized, (5) regardless of the whether or not the carcinoma cells express HER-2/neu, (6) regardless of the extent of expression of HER-2/neu.

The specification teaches that uterine serous papillary carcinoma is a chemoresistant disease with a dismal survival rate. Novel therapeutic strategies effective in the treatment of urine serous papillary carcinoma are desperately needed (p. 2). HER-2/neu is a member of the EGFR family and has been shown to be overexpressed in approximately ½ of primary ovarian carcinomas and breast carcinomas as well as other human tumors including colon, lung, prostate and cervical cancers (p. 3). Recently a humanized monoclonal antibody HERCEPTIN has been reported to have significant therapeutic effects in patient with strongly positive HER-2/neu-positive breast carcinomas (i.e.score of 2+ and 3+). The prior art is deficient in the lack of an effective treatment for uterine serous papillary carcinoma (p. 4). Uterine serous papillary carcinoma cell lines are resistant to nature killer dependent cytotoxicity *in vitro* but are sensitive to HERCEPTIN ADCC. Further, *in vitro* proliferation is significantly inhibited by HERCEPTIN (p. 5). A representative example of an antibody useful in the method of the present invention is HERCEPTIN (p. 12). The specification exemplifies the immunostaining of formalin fixed tumor tissues wherein it is demonstrated that 80% of the uterine serous papillary carcinoma samples overexpressed HER-2/neu at a level of 3+ by immunohistochemical analysis (pages 14-15). HERCEPTIN is an IgG1k that contains human framework regions with CDR regions from a mouse monoclonal antibody that binds to p185 extracellular domain (p. 18). HERCEPTIN was used for most of the studies. For comparison a commercial IgG1 anti-HER2/neu monoclonal antibody was used (p. 18). The

specification exemplifies the sensitivity of uterine serous papillary carcinoma cell lines to HERCEPTIN ADCC and HERCEPTIN mediated inhibition of proliferation (pgs 20, 22, 28, 31, 35, 36) as well as the resistance of the cell lines to NK activity (p. 26, 27, 35).

In the clinical setting, high levels of HER-2/neu in tumor tissue have been associated with shorter patient survival, resistance to chemotherapeutic drugs, resistance to tumor necrosis factor alpha, activated macrophages and killer cells. This study has demonstrated that uterine serous papillary carcinoma commonly overexpresses HER-2/neu (p. 33). The cell line data suggests a correlation between the extremely aggressive biologic behavior of uterine serous papillary carcinoma, their common resistance to standard cytotoxic treatments *in vivo* and their remarkable overexpression of the HER-2/neu receptor (p. 35). Although the majority of previous reports investigating the anti-tumor effects of monoclonal antibodies support the view that efficacy is primarily dependent upon immune activation through the Fc receptor, others have shown that some of the biological effects of HERCEPTIN are independent of Fc receptor binding (p. 39). The present studies show that uterine serous papillary carcinoma express HER-2/neu and are exquisitely sensitive to HERCEPTIN-mediated antibody dependent cellular cytotoxicity. On the basis of these finds and in view of the prior art evidence showing a correlation between efficacy of HERCEPTIN therapy in direct proportion to the HER-2/neu overexpression, it may be postulated that HERCEPTIN is a novel and attractive therapeutic strategy in uterine serous papillary carcinoma patients. The future design and implementation of clinical trials in this regard will ultimately determine the validity of this approach (p. 40).

One cannot extrapolate the teaching of the specification to the scope of the claims because (1) although the specification claims a method using any antibody to HER-2/neu, the specification specifically states that it is HERCEPTIN, and not "any" HER-2/neu antibody, which is postulated as a novel and attractive therapeutic strategy in uterine serous papillary carcinoma patients. It is clear that it is well known in the art that HERCEPTIN is an effective anti-cancer agent in tumors that overexpress HER-2/neu. However, other than stating that this well known antibody, HERCEPTIN, is an example of the claimed antibodies of the invention, the specification does not teach how to make a therapeutic antibody with the properties required for treatment of HER-2/neu overexpressing so that it will function as claimed. For example, Stancovski, et al (PNAS,USA, 88:8691-8695, 1991) characterized the effects of various antibodies that bind the extracellular domain of ErbB2 upon the growth of tumor cells. Stancovski, et al teach, while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the anti-ErbB2 antibodies actually accelerates tumor growth (page 8693, column 1). This phenomenon was also reported in Lewis, et al (Cancer Immunology Immunotherapy 37: 255-263, 1993). US Patent No. 5,677,171 teaches that not every anti-ErbB2 antibody can be used as effectively as monoclonal antibody 4D5 (col 18, lines 15-23). More specifically, '171 teaches that some anti-ErbB-2 antibodies inhibited growth to a lesser extent than Mab 4D5 while others failed to inhibit growth. Further, Strobel, et al (Gynecologic Oncology 73: 362-367, 1999) teach discordant effects of contacting cancer cells with two different neutralizing monoclonal antibodies, i.e., antibodies that block the function of the receptor protein to which they specifically bind (abstract). Despite the fact that both anti-receptor antibodies had been shown to block ligand binding to the receptor, Strobel, et al found that only one of the antibodies could be

used effectively to block cancer cell adhesion to inhibit malignancy. In addition, it is noted that the specification teaches that HERCEPTIN binds to p185 extracellular domain. Clearly one would not expect to be able to practice the claimed invention with an antibody that was not specific for the extracellular domain of HER-2/neu, for example an antibody to the intracellular domain or an antibody that binds only to denatured HER-2/neu, because the antibody would not bind to malignant cells expressing ErbB-2, since the antibody could not contact the intracellular domain of the protein, would not be able to bind to a folded protein and therefore would not inhibit the cells growth and/or proliferation. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

As drawn to (2) cross reactivity of the broadly claimed antibody. It is well known in the art, as taught by Karunagaran et al (EMBO J., 1996, 15:254-264) and Graus-Porta et al (EMBO J., 1997, 16:1647-1655), both of interest and both cited in the specification, that HER-2/neu is a member of the EGFR family and shares homology with other members of the family. Given the shared homology it would be expected that antibodies that are not selective for HER-2/neu would cross react with, and be sequestered by, other members of the EGFR family. In particular it is known that anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the

proper site for the anti-tumor antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the antibody has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

As drawn to claim 1 in particular, (3) monoclonal as opposed to polyclonal antibodies. The claim as written read on not only monoclonal but also polyclonal antibodies. As set forth above, given the identity of HER-2/neu with other members of the EGFR family, it would be expected that a large majority of polyclonal antibodies would bind to epitopes that are shared among members of the EGFR family. These sequestered antibodies would not be available to treat the cancer and it could not be predicted, for the reasons set forth above that the broadly claimed method will function as claimed with a reasonable expectation of success using polyclonal antibodies.

As drawn to claims 1 and 2 in particular (4) non-humanized antibodies. Winter et al (TIPS, 1993, 14:139-143) specifically teach that a major problem with the use of murine monoclonal antibodies in the treatment of human subjects is the development of

human antimouse antibodies (HAMA) that can inactivate the injected antibodies. Thus, it would be expected that the injection of cross species antibody would result in anti-other species antibodies and/or cytotoxic T cells against the injected antibody. Further, Baselga et al (J. Clin. Oncol, 1996, 14:737-744) specifically teach that murine antibodies are limited clinically because they are immunogenic. To facilitate clinical investigations, Mab 4D5 (the murine parent antibody of HERCEPTIN) was humanized. The humanization resulted in a safe treatment which has dose dependent pharmacokinetics in phase I clinical trials (p. 737, col 2). Given the teaching in the art, it could not be predicted and it would not be expected that non-humanized antibodies would function as claimed, that is as a therapeutic for the treatment of uterine serous papillary carcinoma in the human subjects that are clearly contemplated.

As drawn to (5), treatment of uterine serous papillary carcinomas that do not overexpress HER-2/neu, US Patent No. 6,156,321 specifically teaches that among the drawbacks of antibody anti-tumor therapy is that antigen negative cells can survive and repopulate a tumor (col 1, line 64, col 2, line 2). Further Lewis et al, Supra, specifically teach, in Table 2 in *in vitro* studies, that while proliferation of cell lines that over-express ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not over-express ErbB2 was generally unaffected (page 259). Thus, no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed in a uterine serous papillary carcinoma that does not overexpress HER-2/neu. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been

provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

As drawn to (6), treatment of uterine serous papillary carcinoma regardless of the extent of expression of HER-2/neu, Berchuck et al (Am J. Obstet Gynecol., 1991, 164:15-21) examined HER-2/neu expression in endometrial cancers. Berchuck et al specifically teach that normal endometrium expresses HER-2/neu and that staining of the normal endometrium ranges from light to moderate (p. 16, col 2). While 91% of patients with endometrial cancers assayed showed light to moderate staining similar to that seen in the normal patients, 25% of those patients that specifically suffered from uterine serous papillary carcinoma showed heavy staining (p. 17, col 2). Similarly, Saffari et al (Cancer Research, 1995, 55:5693-5698) specifically teach that overexpression of HER-2/neu in endometrial cancers was seen in 33% of the patients that specifically suffered from uterine serous papillary carcinoma (see Table 1, page 5694). However, although a majority of the endometrial cancers assayed did not overexpress HER-2/neu, Pegram et al (J. Clin. Oncol., 1998, 16:2659-2671) specifically teach that Mab 4D5 and HERCEPTIN are known to have antiproliferative activity only against HER-2/neu-overexpressing human breast carcinoma cells *in vitro* and against *in vivo* animal models of breast cancer xenografts with HER-2/neu overexpression *in vivo* (para bridging pgs 2659-2660). Thus it would not be expected and could not be predicted that the successful HERCEPTIN therapy could be used for the treatment of uterine serous papillary carcinomas that did not overexpress HER-2/neu. This *in vitro* and animal model data was shown to correlate with *in vivo* efficacy wherein, Baselga et al, *Supra*, specifically teach that HERCEPTIN is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast

cancers (see abstract). Further, the specification provides no guidance on any antibody that would be effective in the treatment of uterine serous papillary carcinoma that does not overexpress HER-2/neu. In particular, et al (Clinical Cancer Research, 2002, 8:1271-1279) specifically teach that *in vitro* assay of uterine serous papillary cancer cell lines that overexpress HER-2/neu shows that they are highly sensitive to the anti-HER-2/neu ADCC of HERCEPTIN. The reference concludes that on the basis of the sensitivity of the cell lines to HERCEPTIN which is known to specifically target HER-2/neu over-expressing cancer cells, wherein a correlation between efficacy of HERCEPTIN therapy in direct proportion to HER-2/neu expression has been previously demonstrated, that HERCEPTIN might be a novel and attractive therapeutic strategy in the treatment of these patients. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

Finally, it is noted that authors Santin, Bellone, Cannon and O'Brien of the Clinical Cancer Research reference are the inventors of the instant application. The reference was published in May of 2002, eight months after the filing of the instant application and contains much of the data presented in the instant application. The authors conclude that the future design and implementation of clinical trials in this regard will ultimately determine the validity of this approach to the treatment of uterine serous papillary carcinoma. It is clear that at the time the application was filed that the inventors themselves could not predict, in the absence of clinical trials, whether the invention would function as claimed, even with the well known and well characterized

HERCEPTIN therapy. Given the above, it is clear that the inventors could not predict that the broadly claimed antibodies would function as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention. Applicant is invited to submit objective evidence demonstrating that the invention will function as claimed with antibodies other than HERCEPTIN.

8. Claims 4-5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 5 contain the trademark/trade name Herceptin. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe humanized D45 antibody and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 1-5 are rejected under 35 U.S.C. § 103 as being unpatentable over Baselga et al (J. Clin. Oncol., 1996. 14:737-744), in view of Agus et al (Seminars in Oncology, 2000, 27/6 Suppl.11 pages 53-63), Saffari et al (Cancer Research, 1995, 55:5693-5698), Berchuck et al (Am. J. Obstet Gynecol, 164:15-21), Wang et al (Cancer, 1993, 72:28-37) and Pegram et al (J. Clin. Oncol., 1998, 16:2659-2671).

The claims are drawn to a method of treating uterine serous papillary carcinoma in an individual comprising administering a therapeutically effective dose of HER-2/neu antibody, wherein said antibody is a monoclonal antibody, a humanized monoclonal antibody, is HERCEPTIN, is administered in a dose of from about 4 mg/kg to about 8 mg/kg.

Baselga et al teach that HERCEPTIN is a well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancers (see abstract). Previous studies have demonstrated that the parent antibody 4D5 is a potent inhibitor of growth, in vitro and in xenograft models of human breast cancer cells that overexpress HER2 (p. 737, col 20.

Baselga et al teach as set forth, but do not teach a method of treating uterine serous papilloma carcinoma with HERCEPTIN.

Agus et al teach that HER-2/neu is overexpressed in most epithelial malignancies. In preclinical studies with lung, prostate and ovarian tumor cell lines, HERCEPTIN was found to have additive and synergistic effects with some chemotherapeutic agents (see abstract). Clinical trials of HERCEPTIN for the treatment of these diseases are currently underway wherein the dose of HERCEPTIN adminiastered is 4 mg/kg (p. 58, col 2).

Berchuck et al teach that 25% of uterine papillary serous carcinoma assayed overexpress HER-2/neu in comparison with normal controls and most other forms of endometrial cancer (p. 17).

Saffari et al teach that 33% of uterine serous papillary carcinoma assayed overexpress HER-2/neu in comparison with other forms of endometrial cancer (see Table 1, p. 5694).

Wang et al teach that 100% of the uterine serous papillary carcinoma assayed overexpress HER-2/neu in comparison with other forms of endometrial cancer (see Table 1, p. 2631) and normal controls (see p. 2630, col 1).

Pegram et al (J. Clin. Oncol., 1998, 16:2659-2671) specifically teach that Mab 4D5 and HERCEPTIN are known to have antiproliferative activity against HER-2/neu-overexpressing human breast carcinoma cells *in vitro* and against *in vivo* animal models of breast cancer xenografts with HER-2/neu overexpression *in vivo* (para bridging pgs 2659-2660).

It would have been *prima facie* obvious at the time the invention was made to treat a subset of patients with uterine serous papillary carcinoma that overexpress HER-2/neu with HERCEPTIN because Agus et al specifically teach that HER-2/neu is overexpressed in most epithelial malignancies and that in preclinical studies with lung, prostate and ovarian tumor cell lines, HERCEPTIN was found to have additive and synergistic effects with some chemotherapeutic agents and that clinical trials of HERCEPTIN for the treatment of these diseases are currently underway. Given that Pegram et al specifically teach that HERCEPTIN is known to have antiproliferative activity against HER-2/neu-overexpressing human breast carcinoma cells *in vitro* as well as against *in vivo* animal models of breast cancer xenografts with HER-2/neu overexpression *in vivo* and given the absolute correlation of the model data with efficacy in human treatment as taught by Baselga et al one would have a reasonable expectation of success in treating any of lung, prostate and ovarian tumor types which overexpress HER-2/neu and who have shown sensitivity to HERCEPTIN with HERCEPTIN. There is clearly an expectation of success or the long and expensive process of clinical trials would never have been started. Further, given the absolute

correlation of HERCEPTIN sensitivity in *in vitro* studies of tumor cells which overexpress HER-2/neu, the correlation of HERCEPTIN sensitivity with efficacy in treatment and the finding that numerous epithelial cancer types overexpress HER-2/neu and are sensitive to HERCEPTIN, one of ordinary skill in the art would expect that uterine serous papillary carcinoma cells (that is an additional type of epithelial cell cancer) that overexpress HER-2/neu would also be sensitive to HERCEPTIN. Given the above, it would have been *prima facie* obvious to one of ordinary skill in the art to treat any epithelial malignancy that is shown to overexpress HER-2/neu, including uterine serous papillary carcinoma with HERCEPTIN. Given that all of Berchuck et al, Saffari et al and Wang et al specifically teach that at least a subset of patients with uterine serous papillary carcinoma overexpress HER-2/neu, one would have had a reasonable expectation of successfully treating said patients with HERCEPTIN. One would have been motivated to treat said uterine serous papillary carcinoma patients with HERCEPTIN with a reasonable expectation of success because of the correlation already demonstrated between *in vitro* studies and clinical efficacy of HERCEPTIN in tumors that overexpress HER-2/neu. Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the inveniton was made and one would have been motivated to use a dosage of 4 mg/kg of HERCEPTIN since Agus et al specifically teach that this was the dosage used in successful clinical trials.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
October 27, 2003